1-AZA-2-OXA-DIBENZO[*e,h*]AZULENES AND THEIR USE FOR THE TREATMENT OF CENTRAL NERVOUS SYSTEM DISEASES AND DISORDERS

This application is a National Stage under 35 U.S.C. §371 of PCT International Application No. PCT/HR2004/000050, filed November 19, 2004, which claims the benefit under 35 U.S.C. §119(e) of prior Croatian Application No. P20030953A, filed November 21, 2003. The International Application was published in English on Jun. 2, 2005 as WO 2005/049623A1 under PCT Article 21(2).

Field of the Invention

The present invention relates to compounds from the group of 1-aza-2-oxa-dibenzo[*e,h*]azulenes, their pharmacologically acceptable salts and solvates, processes and intermediates for the preparation thereof and to their use in a pharmaceutical compositions for the treatment and prevention of diseases, damages and disorders of the central nervous system (CNS) caused by disorders of the neurochemical equilibrium of biogenic amines or other neurotransmitters.

Background of the Invention

Irregularities in the steady state of biogenic amines (serotonin, norepinephrine, dopamine) and of other neurotransmitters and their receptors that are part of central neurotransmitter system in the CNS may be the cause of various mental diseases, damages and disorders (e.g. depression, schizophrenia, manic behaviour and similar). Pathological changes in the CNS caused by disorders of neurotransmitter concentration may occur due to an unbalanced (too big or too small) synthesis, irregularities in storing, releasing, metabolizing and/or reabsorption of biogenic amines and/or certain neurotransmitters.

The results of investigations directed to the understanding of pathogenesis of mental disorders have shown that a disorder in the serotonin equilibrium plays an important role in various diseases. The monoamine-deficiency hypothesis was one of the first explanations, wherein the symptoms of depression were connected to a reduction in the neurotransmission of monoamines, especially serotonin (5-HT) and noradrenaline, which was also confirmed by neurochemical tests as well as by a successful treatment of the patients with substances increasing monoaminergic neurotransmission (*Expert Opin. Investig. Drugs* **2003**, 12, 531–543). In addition to the serotonergic and noradrenergic systems, a very important role in the CNS function disorders is also played by the dopaminergic system. The understanding of the exact role and of the interactions of these neurotransmitter systems is made rather difficult by the great number of receptor subtypes and their pharmacological

complexity. Thus, it has been observed that e.g. dopaminergic neurotransmission is regulated by 5-HT_{2A} receptors (L. G. Spampinato, *J. Neurochem.* **2000**, *74*, 693–701) and hence 5-HT_{2A} receptors may also be the target receptors in treating diseases and disorders, in whose pathology an important role is played by a disorder of the function of the dopaminergic system (psychoses and various addictions).

Glutamate receptors play a vital role in the mediation of excitatory synaptic transmission as one of the major excitatory neurotransmitters in central nervous system (CNS). It is widely accepted that the σ1 receptor ligands can modulate neurotransmission mediated by central neurotransmitter systems, including glutamatergic/NMDA (F.P. Monnet, G. Debonnel, J.-L. Junien, C. de Montigny, *Eur. J. Pharmacol.*,**1990**, *179*, 441–445). Many pharmacological and physiological actions have been attributed to the σ1 receptor. These include the regulation of IP3 receptors and calcium signaling at the endoplasmic reticulum, mobilization of cytoskeletal adaptor proteins, modulation of nerve growth factor-induced neurite sprouting, modulation of neurotransmitter release and neuronal firing, modulation of potassium channels as a regulatory subunit, alteration of psychostimulant-induced gene expression, and blockade of spreading depression. Behaviorally, the σ1 receptor is involved in learning and memory, psychostimulant-induced sensitization, cocaine-induced conditioned place preference, schizophrenia and pain perception. Thus, it is hypothesized that the σ1 receptor, at least in part, is intracellular amplifier creating a supersensitized state for signal transduction in the biological system.

For treatment of pathological CNS disorders and particularly for mental disorders, the most frequently applied medicines are polycyclic compounds (benzodiazepines, tricyclic and tetracyclic antidepressants, monoamino oxidase (MAO) inhibitors, selective inhibitors of serotonin reabsorption etc.).

A new area in pharmacotherapy was opened by introducing the novel tetracyclic antidepressant mianserin (Claghorn, J.; Lesem, M. D. *Prog. Drug Res.* **1996**, *46*, 243–262; Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). Numerous tetracyclic derivatives showing pharmacological action in the treatment of the disorders of the neurochemical equilibrium in the CNS are disclosed in the literature. WO 99/19317, WO 97/38991 and U.S. 6,511,976 describe the manufacture of tetracyclic derivatives containing tetrahydrofuran ring and the use thereof as substances having antipsychotic, cardiovascular and gastrokinetic actions. U.S. 4,145,434 discloses the manufacture of dibenzo(cyclohepta-, oxepino-, thiepino-)pyrrolidine and dibenzopyrrolidinoazepine derivatives as well as the use thereof as substances having a potential CNS action. The manufacture and an antidepressive action of some 1,2-diazadibenzoazepines are disclosed in EP 0063525. The

manufacture and a potential anxiolytic action of some tetracyclic isooxazolidine derivatives are disclosed as well (*Drugs Fut.* **2002**, 27, Suppl. A: C41; *Drugs Fut.* **2002**, 27, Suppl. A: P182, WO 96/14320, WO 96/14321). The introduction of a piperidine ring into a tetracyclic structure containing an oxepine ring resulted in the formation of the molecule Org-4428 showing an antidepressive action (Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). The molecule Org-5222 contains a pyrrolidine ring fused to an oxepine nucleus and is described as a potential anxiolytic and antipsychotic (Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102). Some derivatives of 1,3-diaza-dibenzo[*e,h*]azulenes and salts thereof as a novel class of compounds with antiinflammatory action are known as well (U.S. 3,711,489, U.S. 4,198,421 and CA 967,573).

There are also known 2-substituted dibenzoazulenes of tetrahydro pyrazole class with substituents such as acyl alkyloxycarbonyl, phenyl or substituted phenyls (Gansser C. et al., Ann. Pharm. **1984**, *41*: 465–471; or Olivera R. et al., *Tetrahedron Letters*, **2000**, *41*: 4353–4356, 4357–4360). Further, there are known examples of dibenzoazepines of pyrazole and isoxazole class substituted with alkyl (Kawashiha K. Takeda, *Kenkyusho Ho*, **1978**, *37*: 6–11, Fishou D. et al., Tetrahedron **1984**, *40*: 5121–5133), phenyl or substituted phenyl (FR 2,504,140, EP 0063525).

However, the known medicines for pathological CNS disorders and particularly for mental disorders are associated with a wide range of adverse effects. Thus, there a need for a safe and effective treatment of diseases and disorders of CNS.

New compounds from the class of 1-aza-2-oxa-dibenzo[*e,h*]azulenes represented by the formula **I**, representing the subject of the present invention, their pharmacologically acceptable salts and solvates and pharmaceutical compositions comprising them have hithero not been described.

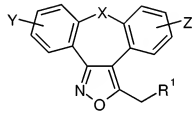
Moreover, no compound representing the subject matter of the present invention has been described as effective in the treatment of diseases and disorders of CNS. Consequently, the use of 1-aza-2-oxa-dibenzo[*e,h*]azulenes and of their pharmaceutically acceptable salts and solvates for use in pharmaceutical compositions for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of neurochemical equilibrium has hitherto been neither disclosed nor suggested.

Summary of the Invention

The compounds from the class of 1-aza-2-oxa-dibenzo[*e,h*]azulenes represented by the formula **I**, differ structurally from the art-known tetracyclic compounds acting upon CNS by an unsaturated tetracyclic structure since they contain an isoxazole ring as the fourth ring, whereas the art-known tetracyclic compounds acting upon CNS (WO 99/19317, WO 97/38991; Sperling, W.; Demling, J. *Drugs Today* **1997**, *33*, 95–102) contain at least one saturated ring in their structure, and are further distinguished by valuable pharmacological and physicochemical properties.

The compounds represeted by the formula **I**, which are the subject matter of the present invention, isomeric forms of such compounds, their pharmaceutically acceptable salts and solvates and pharmaceutical composition comprising them are not believed to have been previously described. Moreover, no compound representing the subject matter of the present invention has been described as effective in the treatment of diseases and disorders of CNS.

The present invention relates to the compounds from the class of 1-aza-2-oxa-dibenzo[*e,h*]azulenes of the general formula **I**:



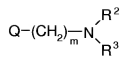
I

wherein

X is CH_2 or a heteroatom selected from the group consisting of O, S, S(=O), S(=O)$_2$ and NR^a, wherein R^a is hydrogen or a substituent selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkanoyl, C_1-C_7-alkoxycarbonyl, C_7-C_{10}-arylalkyloxycarbonyl, C_7-C_{10}-aroyl, C_7-C_{10}-arylalkyl, C_3-C_7-alkylsilyl and C_5-C_{10}-alkylsilylalkyloxyalkyl;

Y and Z independently from each other mean one or more identical or different substituents linked to any available carbon atom selected from the group consisting of hydrogen, halogen , C_1-C_4-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, halo-C_1-C_4-alkyl, hydroxy, C_1-C_4-alkoxy, trifluoromethoxy, C_1-C_4-alkanoyl, amino, amino-C_1-C_4-alkyl, C_1-C_4-alkylamino, *N*-(C_1-C_4-alkyl)amino, *N,N*-di(C_1-C_4-alkyl)amino, thiol, C_1-C_4-alkylthio, sulfonyl, C_1-C_4-alkylsulfonyl, sulfinyl, C_1-C_4-alkylsulfinyl, carboxy, C_1-C_4-alkoxycarbonyl, cyano and nitro;

R^1 is hydrogen, halogen, C_1-C_7-alkyl optionally substituted with one, two, three or more substituents selected from the group consisting of halogen atom, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, N-(C_1-C_4) alkylamino, N,N-di(C_1-C_4-alkyl)-amino, sulfonyl, C_1-C_4 alkylsulfonyl, sulfinyl and C_1-C_4 alkylsulfinyl; C_2-C_7-alkenyl optionally substituted with one, two, three or more halogen atoms; C_2-C_7-alkynyl; monocyclic or bicyclic aryl group having from 6 to 10 carbon atoms and altering double bond and said group can be optionally substituted with one or two substituents selected from the group consisting of fluoro, chloro, C_1-C_4 alkyl, cyano, nitro, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino, *N,N*-di(C_1-C_4-alkyl)-amino, sulfonyl, C_1-C_4 alkylsulfonyl, sulfinyl, C_1-C_4 alkylsulfinyl and can be linked to the rest of the molecule by any available carbon atom via direct bond or via C_1-C_4 alkylene group; monocyclic or bicyclic heteroaryl having the meaning of aromatic and partially aromatic groups of a monocyclic or bicyclic ring with 4 to 12 carbon atoms and at least one of them being heteroatom selected from the group consisting of O, S and N wherein available carbon or nitrogen represent the binding site of the group to the rest of the molecule either via direct bond or via C_1-C_4 alkylene group and where said heteroaryl can be optionally substituted with fluoro, chloro, C_1-C_4 alkyl, cyano, nitro, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino, *N,N*-di(C_1-C_4-alkyl)-amino, sulfonyl, C_1-C_4 alkylsulfonyl, sulfinyl, C_1-C_4 alkylsulfinyl; five-member or six-member fully saturated or partly unsaturated heterocycle group containing at least one hetero atom selected from the group consisting of O, S and N wherein available carbon or nitrogen represent the binding site of the group to the rest of the molecule either via direct bond or via C_1-C_4 alkylene group and where said heterocycle can be optionally substituted with fluoro, chloro, C_1-C_4 alkyl, cyano, nitro, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino, *N,N*-di(C_1-C_4-alkyl)-amino, sulfonyl, C_1-C_4 alkylsulfonyl, sulfinyl, C_1-C_4 alkylsulfinyl; hydroxy; hydroxy-C_2-C_7-alkenyl; hydroxy-C_2-C_7-alkynyl; C_1-C_7-alkoxy; thiol; thio-C_2-C_7-alkenyl; thio-C_2-C_7-alkynyl; C_1-C_7-alkylthio; amino; *N*-(C_1-C_7-alkyl)amino; *N,N*-di(C_1-C_7-alkyl)amino; C_1-C_7-alkylamino; amino-C_2-C_7-alkenyl; amino-C_2-C_7-alkynyl; amino-C_1-C_7-alkoxy; C_1-C_7-alkanoyl; C_7-C_{10}-aroyl; oxo-C_1-C_7-alkyl; C_1-C_7-alkanoyloxy; carboxy; an optionally substituted C_1-C_7-alkyloxycarbonyl; an optionally substituted C_7-C_{10}-aryloxycarbonyl; carbamoyl; *N*-(C_1-C_7-alkyl)carbamoyl; *N,N*-di(C_1-C_7-alkyl)carbamoyl; cyano; cyano-C_1-C_7-alkyl; sulfonyl; C_1-C_7-alkylsulfonyl; sulfinyl; C_1-C_7-alkylsulfinyl; nitro; or a substituent represented with the formula **II**:



II

wherein

R^2 and R^3 simultaneously or independently from each other are hydrogen, C_1-C_4-alkyl, aryl having the meaning as defined above; or together with N are optionally substituted heterocycle or heteroaryl wherein heterocycle relates to five-membere or six-membere fully saturated or partly unsaturated heterocycle group containing at least one hetero atom selected from the group consisting of O, S and N and where said heterocycle can be optionally substituted with one or two substituents which are selected from halogen, C_1-C_4 alkyl, cyano, nitro, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino, *N,N*-di(C_1-C_4-alkyl)-amino, sulfonyl, C_1-C_4 alkylsulfonyl, sulfinyl, C_1-C_4 alkylsulfinyl and heteroaryl relates to aromatic and partially aromatic groups of a monocyclic or bicyclic ring with 4 to 12 carbon atoms and at least one of them being heteroatom selected from the group consisting of O, S and N and where said heteroaryl can be optionally substituted with one or two substituents which are selected from halogen, C_1-C_4 alkyl, cyano, nitro, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino , *N,N*-di(C_1-C_4-alkyl)-amino, sulfonyl, C_1-C_4 alkylsulfonyl, sulfinyl, C_1-C_4 alkylsulfinyl;

m is an integer from 1 to 3;

Q is oxygen, sulfur or nitrogen;

and to their pharmaceutically acceptable salts and solvates, as well as to pharmaceutical compositions containing one or more of the foregoing compounds in an amount effective to treat and prevent diseases, damages and disorders of the central nervous system caused by disorders of neurochemical equilibrium of biogenic amines or other neurotransmitters.

When X is NR^a, R^a relates to hydrogen or group selected from the C_1-C_3-alkyl (preferably methyl or ethyl), C_1-C_3-alkanoyl (preferably formyl or acetyl), C_1-C_7-alkoxycarbonyl (preferably methoxycarbonyl or *tert*-butoxycarbonyl), C_7-C_{10}-arylalkyloxycarbonyl (preferably benzyloxycarbonyl), C_7-C_{10}-aroyl (preferably benzoyl), C_7-C_{10}-arylalkyl (preferably benzyl), C_3-C_7-alkylsilyl (preferably trimethylsilyl) or C_5-C_{10}-alkylsilylalkoxyalkyl (preferably trimethylsilylethoxymethyl).

When R^2 and R^3 together with N are heteroaryl or heterocycle, this means that such heteroaryls or heterocycles have at least one carbon atom replaced by a nitrogen atom through which the groups are linked to the rest of the molecule. Examples of such groups are morpholin-4-yl, piperidin-1-yl, pyrrolidin-1-yl, imidazol-1-yl or piperazin-1-yl.

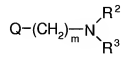
In one embodiment of the present invention preferred compounds of formula **I** are those wherein X represents O or S.

In another embodiment of the present invention preferred compounds of formula **I** are those wherein Y and Z independently from each other mean one or more identical or different substituents linked to any available carbon atom selected from the group consisting of hydrogen, fluorine, chlorine, bromine, C_1-C_4-alkyl (preferably methyl, ethyl, propyl or isopropyl), halo-C_1-C_4-alkyl (preferably trifluoromethyl), hydroxy, C_1-C_4-alkoxy (preferably methoxy), trifluoromethoxy, C_1-C_4-alkanoyl (preferably formyl or acetyl), amino, amino-C_1-C_4-alkyl (preferably aminomethyl), *N*-(C_1-C_4-alkyl)amino (preferably *N*-methyl or *N*-ethyl), *N*,*N*-di(C_1-C_4-alkyl)amino (preferably dimethylamino or diethylamino), thiol, C_1-C_4-alkylthio (preferably methylthio), cyano and nitro.

In yet another embodiment of the present invention preferred compounds of formula **I** are those wherein R^1 is hydrogen, halogen, C_1-C_7-alkyl optionally substituted with one, two, three or more substituents selected from the group consisting of halogen atom, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino and *N*,*N*-di(C_1-C_4-alkyl)-amino; monocyclic or bicyclic aryl group having from 6 to 10 carbon atoms and altering double bond and said group can be optionally substituted with one or two substituents selected from the group consisting of fluoro, chloro, C_1-C_4 alkyl, cyano, nitro, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino and *N*,*N*-di(C_1-C_4-alkyl)-amino and can be linked to the rest of the molecule by any available carbon atom via direct bond or via C_1-C_4 alkylene group; monocyclic or bicyclic heteroaryl having the meaning of aromatic and partially aromatic groups of a monocyclic or bicyclic ring with 4 to 12 carbon atoms and at least one of them being heteroatom selected from the group consisting of O, S and N wherein available carbon or nitrogen represent the binding site of the group to the rest of the molecule either via direct bond or via C_1-C_4 alkylene group and where said heteroaryl can be optionally substituted with fluoro, chloro, C_1-C_4 alkyl, cyano, nitro, hydroxy, C_1-C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino and *N*,*N*-di(C_1-C_4-alkyl)-amino; five-member or six-member fully saturated or partly unsaturated heterocycle group containing at least one hetero atom selected from the group consisting of O, S and N wherein available carbon or nitrogen represent the binding site of the group to the rest of the molecule either via direct bond or via C_1-C_4 alkylene group and where said heterocycle can be optionally substituted with fluoro, chloro, C_1-C_4 alkyl, cyano, nitro, hydroxy, C_1-

C_4 alkoxy, thiol, C_1-C_4 alkylthio, amino, *N*-(C_1-C_4) alkylamino and *N*,*N*-di(C_1-C_4-alkyl)-amino; hydroxy; C_1-C_7-alkoxy; thiol; C_1-C_7-alkylthio; amino; *N*-(C_1-C_7-alkyl)amino; *N*,*N*-di(C_1-C_7-alkyl)amino; amino-C_1-C_7-alkoxy; C_1-C_7-alkanoyl; C_7-C_{10}-aroyl; C_1-C_7-alkanoyloxy; an optionally substituted C_1-C_7-alkyloxycarbonyl; an optionally substituted C_7-C_{10}-aryloxycarbonyl; carbamoyl; *N*-(C_1-C_7-alkyl)carbamoyl; *N*,*N*-di(C_1-C_7-alkyl)carbamoyl; cyano; cyano-C_1-C_7-alkyl; nitro;

or a substituent represented with the formula **II**:



II

wherein

R^2 and R^3 simultaneously or independently from each other are hydrogen, C_1-C_4-alkyl, aryl having the meaning as described above; or together with N are heterocycle or heteroaryl selected from the group consisting of morpholine-4-yl, piperidine-1-yl, pyrrolidine-1-yl, imidazole-1-yl and piperazine-1-yl;

m is an integer from 1 to 3;

Q is oxygen.

In yet another embodiment of the present invention the specifically preferred compounds of formula **I** are:

3-methyl-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulene;

11-chloro-3-methyl-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulene;

3-methyl-2,8-dioxa-1-aza-dibenzo[*e*,*h*]azulene;

3-bromomethyl-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulene;

3-bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulene;

3-bromomethyl-2,8-dioxa-1-aza-dibenzo[*e*,*h*]azulene;

dimethyl-[2-(2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-ethyl]-amine;

dimethyl-[3-(2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-propyl]-amine;

dimethyl-[2-(11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-ethyl]-amine;

dimethyl-[3-(11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-propyl]-amine;

dimethyl-[2-(2,8-dioxa-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-ethyl]-amine; and

dimethyl-[3-(2,8-dioxa-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-propyl]-amine.

Detailed Description of the Invention

The term "halo", "hal" or "halogen" relates to a halogen atom which may be fluorine, chlorine, bromine or iodine.

The term "alkyl" relates to alkyl groups with the meaning of alkanes wherefrom radicals are derived, which radicals may be straight, branched or cyclic or a combination of straight and cyclic ones and branched and cyclic ones. The preferred straight or branched alkyls are e.g. methyl, ethyl, propyl, *iso*-propyl, butyl, *sec*-butyl and *tert*-butyl. The preferred cyclic alkyls are e.g. cyclopentyl or cyclohexyl.

The term "haloalkyl" relates to alkyl groups which must be substituted with at least one halogen atom. The most frequent haloalkyls are e.g. chloromethyl, dichloromethyl, trifluoromethyl or 1,2-dichloropropyl.

The term "alkenyl" relates to alkenyl groups having the meaning of hydrocarbon radicals, which may be straight, branched or cyclic or are a combination of straight and cyclic ones or branched and cyclic ones, but having at least one carbon-carbon double bond. The most frequent alkenyls are ethenyl, propenyl, butenyl or cyclohexenyl.

The term "alkynyl" relates to alkynyl groups having the meaning of hydrocarbon radicals, which are straight or branched and contain at least one and at most two carbon-carbon triple bonds. The most frequent alkynyls are e.g. ethynyl, propynyl or butynyl.

The term "alkoxy" relates to straight or branched chains of alkoxy group. Examples of such groups are methoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

The term "aryl" relates to groups having the meaning of an aromatic ring, e.g. phenyl, as well as to fused aromatic rings. Aryl contains one ring with at least 6 carbon atoms or two rings with a total of 10 carbon atoms and with alternating double (resonant) bonds between carbon atoms. The most freqently used aryls are e.g. phenyl or naphthyl. In general, aryl groups may be linked to the rest of the molecule by any available carbon atom via a direct bond or via a C_1-C_4-alkylene group such as methylene or ethylene.

The term "heteroaryl" relates to groups having the meaning of aromatic and partially aromatic groups of a monocyclic or bicyclic ring with 4 to 12 atoms, at least one of them being a hetero atom such as O, S or N, and the available nitrogen atom or carbon atom is the binding site of the group to the rest of the molecule either via a direct bond or via a C_1-C_4-alkylene group defined earlier. Examples of

this type are thiophenyl, pyrrolyl, imidazolyl, pyridinyl, oxazolyl, thiazolyl, pyrazolyl, tetrazolyl, pirimidinyl, pyrazinyl, quinolinyl or triazinyl.

The term "heterocycle" relates to five-member or six-member, completely saturated or partly unsaturated heterocyclic groups containing at least one hetero atom such as O, S or N, and the available nitrogen atom or carbon atom is the binding site of the group to the rest of the molecule either via a direct bond or via a C_1-C_4-alkylene group defined earlier. The most frequent examples are morpholinyl, piperidyl, piperazinyl, pyrrolidinyl, pirazinyl or imidazolyl.

The term "alkanoyl" group relates to straight chains of acyl group such as formyl, acetyl or propanoyl.

The term "aroyl" group relates to aromatic acyl groups such as benzoyl.

The term "optionally substituted alkyl" relates to alkyl groups which may be optionally additionally substituted with one, two, three or more substituents. Such substituents may be halogen atom (preferably chlorine or fluorine), hydroxy, C_1-C_4-alkoxy (preferably methoxy or ethoxy), thiol, C_1-C_4-alkylthio (preferably methylthio or ethylthio), amino, *N*-(C_1-C_4-alkyl)amino (preferably *N*-methylamino or *N*-ethylamino), *N,N*-di(C_1-C_4-alkyl)amino (preferably dimethylamino or diethylamino), sulfonyl, C_1-C_4-alkylsulfonyl (preferably methylsulfonyl or ethylsulfonyl), sulfinyl, C_1-C_4-alkylsulfinyl (preferably methylsulfinyl).

The term "optionally substituted alkenyl" relates to alkenyl groups optionally additionally substituted with one, two or three halogen atoms. Such substituents may be e.g. 2-chloroethenyl, 1,2-dichloroethenyl or 2-bromo-propen-1-yl.

The term "optionally substituted aryl, heteroaryl or heterocycle" relates to aryl, heteroaryl or heterocyclic groups which may be optionally additionally substituted with one or two substituents. The substituents may be halogen (preferably chlorine or fluorine), C_1-C_4-alkyl (preferably methyl, ethyl or isopropyl), cyano, nitro, hydroxy, C_1-C_4-alkoxy (preferably methoxy or ethoxy), thiol, C_1-C_4-alkylthio (preferably methylthio or ethylthio), amino, *N*-(C_1-C_4)alkylamino (preferably *N*-methylamino or *N*-ethylamino), *N,N*-di(C_1-C_4-alkyl)amino (preferably *N,N*-dimethylamino or *N,N*-diethylamino), sulfonyl, C_1-C_4-alkylsulfonyl (preferably methylsulfonyl or ethylsulfonyl), sulfinyl, C_1-C_4-alkylsulfinyl (preferably methylsulfinyl).

Depending upon the nature of particular substituents, the compounds of the formula **I** may have geometric isomers and one or more chiral centres so that there can exist enantiomers or

diastereoisomers. The present invention also relates to use of such isomers and mixtures thereof, including racemates.

The present invention also relates to all possible tautomeric forms of particular compounds of the formula **I**.

Whenever used hereinafter, the term "compounds of formula **I**" or "compounds of the present invention" is meant to also include the pharmaceutically acceptable addition salts and solvates.

The term "salts" can include acid addition salts or addition salts of free bases. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include but are not limited to salts derived from nontoxic inorganic acids such as nitric, phosphoric, sulfuric, or hydrobromic, hydroiodic, hydrofluoric, phosphorous, as well as salts derived from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxyl alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, and acetic, maleic, succinic, or citric acids. Non-limiting examples of such salts include napadisylate, besylate, sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S. M. et al. "Pharmaceutical Salts," J. of Pharma. Sci., 1977; 66:1).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine,

chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid.

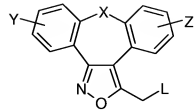
Preferred pharmaceutically acceptable salts according to invention relate to salts of the formula **I** and include e.g. salts with C_1-C_4-alkylhalides (preferably methyl bromide, methyl chloride) (quaternary ammonium salts), with inorganic acids (hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric or sulfuric acids) or with organic acids (tartaric, acetic, citric, maleic, lactic, fumaric, benzoic, succinic, methane sulfonic or *p*-toluene sulfonic acids).

Pharmaceutically acceptable solvates formed by the compounds represented by formula **I** or their salts relate to hydrates, ethanolates and similar (most frequently hydrates).

The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopeias for use in mammals, and more particularly in humans.

A further object of the present invention relates to the preparation of the compounds of the formula **I** according to the following processes:

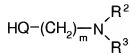
a) condensation of compound **Ia**:



Ia

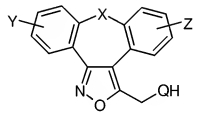
wherein X, Y and Z have the earlier stated meanings, L is a leaving group,
with an optionally selected alcohol, thioalcohol or amine or with a compound of the formula **IIa**:

IIa



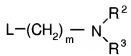
wherein all radicals and symbols have the earlier stated meanings;

b) condensation of compound of the formula **Ib**:



Ib

wherein all symbols have the earlier stated meanings, with a compound of the formula **IIb**:



IIb

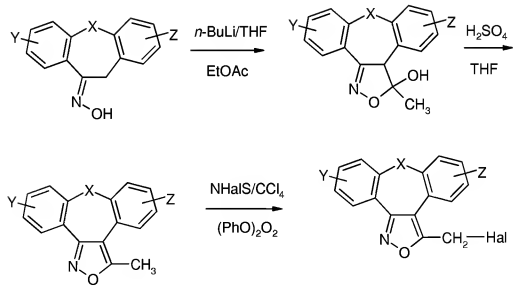
wherein radicals R^2 and R^3 and symbol m have the earlier stated meanings and symbol L is a good leaving group. Suitable leaving groups for these reactions include halide (e.g. chloride, bromide or iodide).

Preparation methods

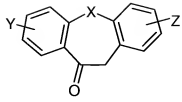
a) Compounds of the formula **I** according to the present process are prepared by reaction of compounds of the formula **Ia**, wherein L is a leaving group, with optionally selected alcohols, thioalcohols or amines, or with compounds of the formula **IIa**, wherein Q is oxygen, nitrogen or sulfur. The condensation reactions may be carried out most conveniently according to methods disclosed for the preparation of analogous compounds (Menozzi G et al., *J. Heterocyclic Chem.*, **1997**, *34*:963-968 or WO 01/87890). The reactions are carried out at a temperature from 20°C to 100°C during 1 to 24 hours in a two-phase system (preferably with 50% NaOH/toluene), sometimes in the presence of a phase transfer catalyst (preferably benzyl triethyl ammonium chloride, benzyl triethyl ammonium bromide, cetyl trimethyl bromide). After the treatment of the reaction mixture, the products formed are isolated by recrystallization or chromatography on a silica gel column.

The starting compounds of the formula **Ia** (most frequently halides) may be obtained by the reaction sequence represented in Scheme I according to the processes described for analogous compounds (Talley J. J. et al., *J. Med. Chem.*, **2000**, *43*: 775–777).

Scheme I



Hydroxylamines required for the above reaction sequence are compounds known from the literature or are prepared by the action of $NH_2OH \cdot HCl$ upon ketones



in the presence of NaOAc in an alcohol-aqueous medium.

The starting alcohols, thioalcohols or the compounds of the formula **IIa** are commercially available substances or are prepared according to methods disclosed for the preparation of analogous compounds.

b) The compounds of the formula **I** may be prepared according to the present process by condensation of compounds of formula **Ib** with optionally selected halides or with compounds of formula **IIb**, wherein L is a leaving group. The condensation reactions are reactions of nucleophilic substitution on saturated carbon atom, which are described in the literature and are carried out in an analogous manner as described in method a).

The starting compounds, alcohols of the formula **Ib,** may be obtained by the action of water, ammonia or hydrogen sulfide upon halides of formula **Ia** in a manner disclosed in the literature. The starting optionally selected halides or compounds of the formula **IIb** are already known or are prepared according to methods disclosed for the preparation of analogous compounds.

Besides the above-mentioned reactions, the compounds of the formula **I** may be prepared by the transformation of other earlier prepared compounds of the formula **I** and it is to be understood that the present invention also comprises such compounds and processes. An example of such transformation is a reaction of the aldehyde group with chosen phosphorous ylides resulting in a prolongation of the chain and the formation of an alkenyl substituent with carbonyl or ester groups as disclosed in WO 01/87890. These reactions are carried out in solvents such as benzene, toluene or hexane at elevated temperature (most frequently at boiling temperature of the solvent).

A further general example of transformation is formylation of the compounds of the formula **I** by processes such as e.g. Vilsmeier acylation or reaction of *n*-BuLi and dimethylformamide. The reaction conditions of these processes are known in the literature.

By hydrolysis of the compounds of the formula **I** having nitrile, amide or ester groups, there may be prepared compounds with a carboxyl group, which are suitable intermediates for the preparation of other compounds with novel functional groups such as e.g. esters, amides, halides, anhydrides, alcohols or amines.

Oxidation or reduction reactions are a further possibility of the change of substituents in the compounds of the formula **I**. Most frequently used oxidation agents are peroxides (hydrogen peroxide, *m*-chloroperbenzoic acid or benzoyl peroxide) or permanganate, chromate or perchlorate ions. Thus e.g. by the oxidation of an alcohol group by pyridinyl dichromate or pyridinyl chlorochromate, an aldehyde group is formed, which group may be converted to a carboxyl group by further oxidation.

By a selective oxidation of alkylthio group, alkylsulfinyl or alkylsulfonyl groups may be prepared.

By the reduction of the compounds with a nitro group, the preparation of amino compounds is made possible. The reaction is carried out under usual conditions of catalytic hydrogenation or electrochemically. By catalytic hydrogenation using palladium on carbon, alkenyl substituents may be converted to alkyl ones or nitrile group can be converted to aminoalkyl.

Various substituents of the aromatic structure in the compounds of the formula **I** may be introduced by standard substitution reactions or by usual changes of individual functional groups. Examples of such reactions are aromatic substitutions, alkylations, halogenation, hydroxylation as well as oxidation or reduction of substituents. Reagents and reaction conditions are known from the literature. Thus e.g. by aromatic substitution a nitro group is introduced in the presence of concentrated nitric acid and sulfuric acid. By using acyl halides or alkyl halides, the introduction of an acyl group or an alkyl group is made possible. The reaction is carried out in the presence of Lewis acids such as aluminum- or iron-trichloride in conditions of Friedel-Craft reaction. By the reduction of the nitro group, an amino group is obtained, which is by a diazotizing reaction converted to a suitable starting group, which may be replaced with one of the following groups: H, CN, OH, Hal.

In order to prevent undesired interaction in chemical reactions, it is often necessary to protect certain groups such as e.g. hydroxy, amino, thio or carboxy. For this purpose a great number of protecting groups may be used [Green TW, Wuts PGH, Protective Groups in Organic Synthesis, John Wiley and Sons, 1999)] and the choice, use and elimination thereof are conventional methods in chemical synthesis.

A convenient protection for amino or alkylamino groups are groups such as e.g. alkanoyl (acetyl), alkoxycarbonyl (methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl); arylmethoxycarbonyl (benzyloxycarbonyl), aroyl (benzoyl) or alkylsilyl (trimethylsilyl or trimethylsilylethoxymethyl) groups. The conditions of removing a protecting group depend upon the choice and the characteristics of this group. Thus e.g. acyl groups such as alkanoyl, alkoxycarbonyl or aroyl may be eliminated by hydrolysis in the presence of a base (sodium hydroxide or potassium hydroxide), *tert*-butoxycarbonyl or alkylsilyl (trimethylsilyl) may be eliminated by treatment with a suitable acid (hydrochloric, sulfuric, phosphoric or trifluoroacetic acid), whereas arylmethoxycarbonyl group (benzyloxycarbonyl) may be eliminated by hydrogenation using a catalyst such as palladium on carbon.

The compounds of the present invention are especially effective in treating those diseases and disorders where the neurochemical equilibrium of biogenic amines such as serotonin, norepinephrine and dopamine was disturbed and which may be caused by unbalanced (too big or too small) synthesis, irregularities in storing, releasing, metabolizing and/or reabsorption of a certain neurotransmitter.

It has been found that the compounds of the present invention exhibit a significant binding affinity and have a high degree of selectivity to serotonin receptors, especially to 5-HT_{2A} and 5-HT_{2C}, as well as for the σ1 receptor.

In one embodiment of the present invention the compound of formula **I**, or salt, or solvate thereof show binding affinity to 5-HT_{2A} and 5-HT_{2C} serotonin receptors in the concentration expressed as an IC_{50} value less than 1 μM and having K_i value less than 1 μM.

In another embodiment of the present invention the compound of formula **I**, or salt, or solvate thereof show binding affinity to 5-HT_{2A} serotonin receptor in the concentration expressed as an IC_{50} value less than about 200 nM and having K_i value less than about 100 nM.

In yet another embodiment of the present invention the compound of formula **I**, or salt, or solvate thereof show binding affinity to 5-HT_{2C} serotonin receptor in the concentration expressed as an IC_{50} value less than about 200 nM and having K_i value less than about 100 nM.

It has been found that the compounds of the present invention exhibit a significant binding affinity to the σ1 receptor.

In one embodiment of the present invention the compound of formula **I**, or salt, or solvate thereof show binding affinity to the σ1 receptor in the concentration expressed as an IC_{50} value less than 1 μM and having K_i value less than 1 μM.

In another embodiment of the present invention the compound of formula **I**, or salt, or solvate thereof show binding affinity to the σ1 receptor in the concentration expressed as an IC_{50} value less than about 200 nM and having K_i value less than about 100 nM.

Since serotonin receptors are crucial in pathophysiology of a series of CNS disorders (directly or indirectly by participating in the activation of some other neurotransmitter e.g. dopamine and/or receptor), the compounds of the present invention may be used in pharmaceutical formulations for the treatment and prevention of diseases, damages and disorders, wherein biogenic amines and their receptors play an important role.

In view of the above explained favourable biological properties of the compounds of the present invention administration of the therapeutically effective amount of a compound of formula **I** provides an effective method of treatment of CNS diseases and disorders associated with fewer side effects due to their improved selectivity towards the the σ1 receptor and the 5-HT_{2A} and 5-HT_{2C} serotonin receptors.

Pharmaceutical Compositions

In general, the compounds of the present invention may be used in pharmaceutical formulations that are used as antidepressants, anxiolytics, antipsychotics or as drugs for treating migraine.

Further, the compounds of the present invention may be used in pharmaceutical formulations for the treatment and prevention of diseases and disorders which are the result of disorders of neurochemical equilibrium in the central nervous system such as e.g. depression and modest depression, anxiety, bipolar disorders, sleeping disorders, sexual disorders, psychoses, borderline psychoses, schizophrenia, migraine, personality disorders and obsessive-compulsive disorders, social phobias or panic attacks, organic mental disorders in children, aggression, memory disorders and personality disorders in elderly people, addiction, obesity, bulimia and similar disorders, snoring, premenstrual troubles.

Likewise, these compounds may be used in the treatment and/or prevention of CNS damage caused by trauma, brain stroke, neurodegenerative diseases, cardiovascular disorders such as high blood pressure, thrombosis, infarct and similar diseases as well as in gastrointestinal disorders.

The effective dose of the active substance of the present invention and of a pharmaceutically acceptable salt or solvate thereof depends on the efficacy of the compound of the general formula **I**, on the nature and the severity of the disease and the disorder of CNS as well as on the body weight of the patient treated and may be from 0.001–10 mg/kg body weight. In any case a unit dose for an adult of an average weight of 70 kg is understood to be 0.07–1000 mg of the compound of the general formula **I** or of a pharmaceutically acceptable salt or solvate thereof. A unit dose may be administered once or several times daily, e.g. 2, 3 or 4 times daily, most frequently 1 to 3 times daily.

The present invention more specifically relates to an effective dose of the compounds which bind to serotonin, sigma, adrenergic, dopamine or muscarinic receptors and/or act as inhibitors of reabsorption of one or more biogenic amines (serotonin, dopamine, norepinephrine).

Further, the present invention relates to a pharmaceutical formulation containing an effective non-toxic dose of the compounds of the present invention as well as pharmaceutically acceptable carriers or solvents.

The pharmaceutical formulations are obtained by blending a therapeutically active amount of a certain substance as the active ingredient with a pharmaceutically acceptable carrier, which may have different forms depending on the desired administration route. These pharmaceutical formulations especially relate to oral, sublingual, rectal, percutaneous or parenteral administration route.

Pharmaceutical formulations may be manufactured using conventional pharmaceutical auxiliaries and manufacture routes. Forms for oral administration may be syrups, capsules, tablets and similar forms where usual solid carriers are inert substances such as lactose, starch, glucose, methylcellulose, magnesium stearate, dicalcium phosphate, mannitol and similar, and usual liquid oral auxiliaries include ethanol, glycerol, water and similar. All auxiliaries may be optionally blended with disintegrants, diluents, granulating agents, wetting agents, binders and similar by using conventional methods. Parenteral forms may be manufactured by using water or some other sterile carrier. When in oral formulations some of the common liquid carriers e.g. water, glycol, oils, alcohols and similar are used, the formulation may be in the form of syrup, emulsion, soft gelatine capsules or sterile injectable liquids e.g. ampoules, or of non-aqueous liquid suspensions. When for the manufacture of oral formulations a solid carrier such as starch, sugar, kaolin, wetting agents, binders, disintegrants

and similar is used, the formulation may be in the form of a powder, capsule, tablet, hard gelatine capsules or granules that may be administered in capsules, and the amount of the solid carrier may vary (most frequently from 1 mg to 1 g). Due to their easy use, tablets and capsules are the most convenient oral formulations wherein a solid carrier is used. For parenteral formulations the carrier is mostly sterile water, though other ingredients may be contained therein as well in order to improve solubility. For the manufacture of injectable solutions, sodium chloride solution, glucose solution or a mixture thereof is used. Injectable solutions may also contain a component for a delayed release of active component. Convenient oils that may be used for this purpose are e.g. arachic oil, sesame oil, cottonseed oil, corn oil, soybean oil, synthetic glycerol esters of long-chain fatty acids or a mixture of some of said oils. Injectable suspensions may be manufactured in such a way that a suitable liquid carrier used is blended with a suspending agent. In formulations convenient for percutaneous administration, as a carrier there is understood a substance improving the penetration of the active substance and/or a suitable wetting agent, which may be combined with a suitable additive of any provenience, which additives do not cause harmful effects on skin. Said additives may facilitate the skin administration and/or may be used in the manufacture of the desired formulations, which may be applied in various ways e.g. transdermally, spot-on, or in the form of an ointment.

To improve the solubility and/or stability of the present compounds, in pharmacological formulations there may be used α-, β- or γ-cyclodextrins or derivatives thereof, especially hydroxyalkyl substituted cyclodextrins i.e. 2-hydroxypropyl-β-cyclodextrin. Cosolvents such as e.g. alcohols may also improve the solubility and/or stability of the present compounds in various pharmaceutical formulations.

The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. However, since memantine is highly soluble, aqueous solutions are preferred. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, 18th Edition. Particularly preferred for the present invention are carriers suitable for immediate-release, i.e., release of most or all of the active ingredient over a short period of time, such as 60 minutes or less, and make rapid absorption of the drug possible.

A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise

undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the present application includes both one and more than one such excipient.

"Treating" or "treatment" of a state, disorder or condition includes:

(1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition,

(2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or

(3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

Dosages and administration regimen can be adjusted depending on the age, sex, physical condition as well as the benefit acchieved by applying the compounds of the present invention and the side effects in the patient or the mammalian subject to be treated and the judgement of the physician, as is appreciated by those skilled in the art.

The term host or subject in need thereof as used herein refers to a mammal preferably a human.

Biological Assays

The effect of the compounds of the present invention on the neurochemical steady state was determined by *in vitro* investigations such as a radionuclide-marked radioligand binding assay for 5-HT_{2A} (Bonhaus D. W. Br. *J. Pharmacol.* **1995**, *115*:622; Saucier C. *J. Neurochem.* **1997**, *68*:1998) and 5-HT_{2C} receptors (Wolf W. A. *J. Neurochem.* **1997**, *69*:1449), *in vitro* binding assay for the σ1 receptor (Thomson W. and Donn R. *Arthritis Res.* **2002**, 4: 302-306) and by *in vivo* investigations in a

tail suspension test (Vogel H. G. and Vogel W. H. Drug Discovery and Evaluation Pharmacological Assays, Springer **1997,** 304), in amphetamine-induced hyperlocomotion in mice (Millan M.J. et al, **1998** *J Pharmacol. Exp. Ther.* 287: 167-186), in a forced swim test in mice (Porsolt R. D. et al. *Arch. Int. Pharmacodyn.* **1977**, *229*:327–336), in meta-chlorophenyl piperazine (m-CPP) test on rats (*Drug Dev. Res.* **1989**, *18*:119–144), and in apomorphine, tryptamine, norepinephrine (ATN) test in rats (*Arch. Int. Pharmacodyn.* **1977**, *227*:238–253).

In *vitro* method for determining affinity for binding to 5-HT_{2A} and 5-HT_{2C} receptors

A small concentration of a radioligand having a great affinity for binding to a receptor was incubated with a tissue sample enriched with a certain receptor (1–5 mg of tissue) in a buffered medium (0.2–5 mL). Recombinant human HT_{2A} and HT_{2C} receptors were expressed in CHO-K1 or COS-7 cells and were also used for competitive binding. During incubation the radioligand bound to the receptor. When a binding balance was achieved, the receptors to which the radioligand was bound were separated from those to which said ligand was not bound, and the radioactivity of the receptor/radioligand complex was measured. The interaction of the tested compounds with receptors was tested in competitive binding experiments. Various concentrations of tested compounds were added to the incubation mixture containing a prepared tissue enriched with corresponding receptors and the radioligand. The radioligand binding was inhibited by the test compounds proportionally to the affinity of a certain compound for the receptor and to the concentration of the compound.

The radioligand used for the determination of binding to 5-HT_{2A} receptor was [^{3}H]-ketanserin and the tissue used was human cortex or recombinant 5-HT_{2A} receptor expressed in CHO-K1 cells.

The radioligand used for the determination of binding to 5-HT_{2C} receptor was [^{3}H]-mesulergine and the tissue used was choroid plexus or recombinant 5-HT_{2C} receptor expressed in CHO-K1 cells.

Compounds showing IC_{50} and K_i values lower than 1 μM, were considered to be active.
Compounds: 3-methyl-2-oxa-8-thia-1-aza-dibenzo[e,h]azulene and dimethyl-[3-(2-oxa-8-thia-1-aza-dibenzo[e,h]azulen-3-ylmethoxy)-propyl]-amine showed binding affinity to 5-HT_{2A} and 5-HT_{2C} serotonin receptors expressed as IC_{50} value less than 200 nM and Ki value less than 100 nM.
It is anticipated that similar results will be observed for other compounds of the invention.

In *vitro* method for determining binding affinity to the σ1 receptor

Jurkat cell were grown in medium, RPMI supplemented with 10% fetal bovine serum, 100U/ml penicillin and 100μg/ml streptomycin, collected and their suspension homogenized. After centrifugation, membrane fraction was separated, resuspended in phosphate buffer (pH=7.5) and stored in small aliquots in liquid nitrogen until use.

Binding of different radiolabeled ligands to Jurkat cell membranes was measured as described previously (Ramamoorthy et al., 1995). To characterize the σ binding sites in the Jurkat cell line, [^{3}H]haloperidol as first used as the ligand. Haloperidol is a high affinity ligand to both type 1 and type 2 σ-receptors. The binding assays were done using Jurkat cell membranes in the presence of [^{3}H]haloperidol (10nM) alone to determine the total binding, and in the presence of [^{3}H]haloperidol (10nM) and unlabeled haloperidol (10μM) to determine the nonspecific binding.

Membranes were incubated with ligands in phosphate buffer for 3 hours at room temperature. After filter had been washed, radioactivity associated with the filter was determined by liquid scintillation spectrometry.

Compounds showing IC_{50} and K_i values lower than 1 μM, were considered to be active.

It is anticipated that similar results will be observed for other compounds of the invention.

Forced swim test in mice

Male CD1 mice of the weight of 20–25 g were used for the experiment. Groups of 10 animals were treated with the test compounds, imipramine (positive control) or the vehicle (negative control) by *per os* by gavage 30 min prior to testing to determine efficacy. On the day of the experiment the animals were placed into a glass cylinder (height 18.2 cm, diameter 13.3 cm) filled with water warmed to 22 °C to the height of 10 cm. The immobility defined as the end of the struggling of the animal and the beginning of floating, wherein the movements were reduced to those indispensable for the animal to keep its head over the water surface, started to be recorded after two minutes and then it was monitored during 4 minutes.

The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a carrier. The compounds that in a dose of 10 mg/kg reduced the immobility of animals for 30 % and more over the control group were considered to be active.

It is anticipated that similar results will be observed for other compounds of the invention.

Tail suspension test in mice

Male Balb/cJ mice of the weight of 20–25 g were used for the experiment. Groups of 9 animals were treated with the test compounds, imipramine (positive control) or the vehicle (negative control) by intraperitoneal injection, subcutaneous injection or per oral by gavage 30 min prior to testing to measure potential antidepressant activity. Mice were suspended from their tails at a height of about 90 cm and were observed for 5 minutes. The mice hanging fully motionless for 1 minute during the observation period were defined as depressive. In animals treated with a substance having an antidepressive action the period of immobility was shortened.

The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a vehicle. Significance of results was analysed using Fischer's exact test. The compounds that in a dose of 10 mg/kg reduced the immobility of animals for 40 % and more over a control group were considered to be active.
It is anticipated that similar results will be observed for other compounds of the invention.

Amphetamine-induced hyperlocomotion in mice

Male Swiss OFA mice of a weight 30-35g were treated with either vehicle (saline) or test compounds 30 minutes prior to hyperlocomotion induction. Dexamphetamine sulphate was administered intraperitoneally at 2mg/kg. Thirty minutes later, animals were placed in a wooden box 80 x80 cm in a room with low light intensity (100 lux) for locomotor activity recording. Locomotor activity was determined during a 30 min period using a video image analyzer. Total duration of movement, occurence of movement and total distance travelled were measured. Haloperidol was tested at the dose of 0,25 mg/kg (prepared in 0,5% methylcellulose) and served as reference substance.

Compounds were considered as active if in a dose of 10 mg/kg reduced amphetamine-induced hyperlocomotion in experimental animals for 30% and more when compared to vehicle treated control group.
It is anticipated that similar results will be observed for other compounds of the invention.

Meta-chlorophenyl piperazine (m-CPP) test on rats

The tested substance was administered to rats *per os* 1 hour before the test and m-CPP in a dose of 1 mg/kg was administered intravenously 15 minutes before the test. At the beginning of the experiment the treated animals were subjected to an open field test on rats (*Drug Dev. Res.* **1989**, 18, 119–144):

the apparatus consisted of an open box having the dimensions 80 × 65 × 35 cm, which in one wall had an opening with a diameter of 10 cm, by which it was connected to a non-illuminated compartment having the dimensions 25 × 21 × 21 cm, and the opening was illuminated by a light source (IR source or Kleverlux®; 12 V/20 W) from the distance of 66 cm; one hour after administering the tested substance, the animals were placed in the dark (non-illuminated) compartment so that their heads were turned away from the illuminated exit and the passing of the animals from the dark compartment to the illuminated one was measured for 10 minutes.

As an active dose of the substance there was defined a dose at which the effect induced by m-CPP was reduced for 40 % and more.
It is anticipated that similar results will be observed for other compounds of the invention.

Apomorphine, tryptamine, norepinephrine (ATN) test in rats

At the beginning of the experiment (t = 0) the animals were injected intravenously by 1.25 mg/kg of apomorphine, then by 40 mg/kg of tryptamine (t = 60 minutes) and by 1.25 mg/kg of norepinephrine (t = 90 minutes).

There were watched a state of exceptional agitation and normal behaviour during 60 minutes (apomorphine test), then bilateral clonic convulsions of back paws and a general tremor of the body in tryptamine test (observation period 5 minutes) and lethality during 120 minutes after the injection in norepinephrine test.

The percentage of animals showing a passive behaviour was calculated and compared with a control group treated with a carrier.

The compounds which in a dose of 10 mg/kg reduced the period of duration of observed effects (mobility) for 40 % over a control group were considered to be active in *in vivo* testings.
It is anticipated that similar results will be observed for other compounds of the invention.

Some of the present compounds tested in the above assays showed an action in at least two of said tests, though these results represent only an illustration of the biological action of the compounds and do not limit the present invention in any way.

Examples

The present invention is illustrated by the following Examples which are in no way a limitation thereof.

Example 1

*3-Methyl-3,3a-dihydro-2-oxa-8-thia-1-aza-*dibenzo[e,h]*azulen-3-ol* (**1a**)

To a solution of 11H-dibenzo[*b,f*]thiepin-10-one oxime (1.66 mmole) in dry THF (10 mL) cooled to –78 °C, n-butyl lithium (3.57 mmole) was slowly added drop by drop. The reaction mixture was stirred for 15 minutes at this temperature, whereupon it was heated to 0 °C and ethyl acetate (3.57 mmole) was added thereto. The stirring of the reaction mixture was continued for 1 more hour at room temperature, whereupon water was added and it was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

^{1}H NMR (ppm, $CDCl_3$): 2.03 (s, 3H), 7.27-7.60 (m, 8H);

MS (*m/z*): 306.1 [MNa^+], 338.1 [MNa^+ + MeOH].

3-Methyl-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulene* (**1**)

To a solution of 3-methyl-3,3a-dihydro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ol (**1a**) (0.07 mmole) in THF (5 mL), concentrated sulfuric acid (100 µL) was added. The reaction mixture was stirred and heated under reflux for 5 hours, then it was cooled and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, an oily product was isolated;

^{1}H NMR (ppm, $CDCl_3$): 2.74 (s, 3H), 7.35-7.93 (m, 8H);

MS (*m/z*): 265.9 [MH^+].

Example 2

3-Methyl-3,3a-dihydro-11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ol* (**2a**)

To a solution of 11-chloro-11H-dibenzo[*b,f*]thiepin-10-one oxime (1.89 mmole) in dry THF (10 mL) cooled to –78 °C, n-butyl lithium (4.07 mmole) was slowly added drop by drop. The reaction mixture was stirred for 15 minutes at this temperature, whereupon it was heated to 0 °C and ethyl acetate (4.07 mmole) was added thereto. The stirring of the reaction mixture was continued for 1 more hour at room temperature, whereupon water was added and it was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 340.1 [MNa^+].

3-Methyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulene* (**2**)

To a solution of 3-methyl-3,3a-dihydro-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ol (2a) (0.08 mmole) in THF (5 mL), concentrated sulfuric acid (114 μL) was added. The reaction mixture was stirred and heated under reflux for 5 hours, then it was cooled and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, an oily product was isolated;

MS (*m/z*): 300.78 [MH^+].

Example 3

3-Methyl-3,3a-dihydro-2,8-dioxa-1-aza-dibenzo[e,h]*azulen-3-ol* (**3a**)

To a solution of 11H-dibenzo[*b,f*]oxepin-10-one oxime (1.91 mmole) in dry THF (10 mL) cooled to – 78 °C, n-butyl lithium (4.10 mmole) was slowly added drop by drop. The reaction mixture was stirred for 15 minutes at this temperature, whereupon it was heated to 0 °C and ethyl acetate (4.10 mmole) was added. The stirring of the reaction mixture was continued for one more hour at room temperature, whereupon water was added thereto and it was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 290.3 [MNa^+].

3-Methyl-2,8-dioxa-1-aza-dibenzo[e,h]*azulene* (**3**)

To a solution of 3-methyl-3,3a-dihydro-2,8-dioxa-1-aza-dibenzo[*e,h*]azulen-3-ol (**3a**) (0.1 mmole) in THF (7 mL), concentrated sulfuric acid (143 μL) was added. The reaction mixture was stirred and heated under the reflux for 5 hours, then it was cooled and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, an oily product was isolated;

MS (*m/z*): 250.27 [MH^+].

Example 4

1-Bromomethyl-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulene* (**4**)

To a solution of 3-methyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**1**) (0.68 mmole) in carbon tetrachloride (15 mL), NBS (N-bromosuccinimide) (1.02 mmole) and a catalytic amount of benzoyl peroxide $(PhCO)_2O_2$ were added. The reaction mixture was stirred and heated under the reflux for 6–8

hours, then it was cooled, the precipitated succinimide was filtered and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, an oily product was isolated;

^{1}H NMR (ppm, $CDCl_3$): 4.63 (s, 2H), 7.38-8.10 (m, 8H);

MS (*m/z*): 264.0 [M-Br].

Example 5

1-Bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulene* (**5**)

To a solution of 3-methyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**2**) (0.78 mmole) in carbon tetrachloride (15 mL), NBS (N-bromosuccinimide) (1.17 mmole) and a catalytic amount of benzoyl peroxide $(PhCO)_2O_2$ were added. The reaction mixture was stirred and heated under reflux for 6–8 hours, then it was cooled, the precipitated succinimide was filtered and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 298.45 [M-Br].

Example 6

1-bromomethyl-2,8-dioxa-1-aza-dibenzo[e,h]*azulene* (**6**)

To a solution of 3-methyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene (**3**) (0.58 mmole) in carbon tetrachloride (15 mL), NBS (N-bromosuccinimide) (0.87 mmole) and a catalytic amount of benzoyl peroxide $(PhCO)_2O_2$ were added. The reaction mixture was stirred and heated under reflux for 6–8 hours and cooled, the precipitated succinimide was filtered and the solvent was evaporated, water was added thereto and it was extracted with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 248.0 [M-Br].

Example 7

Dimethyl-[3-(2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-propyl]-amine* (**7**)

To a solution of 3-dimethylaminopropylchloride-hydrochloride (2.16 mmole) in 50 % sodium hydroxide (1.9 mL), a catalytic amount of benzyltriethylammonium chloride and a solution of 1-bromomethyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**4**) (0.15 mmole) in toluene (10 mL) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours, then it was cooled to room temperature, diluted with water and extracted with dichloromethane. The organic

extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;
MS (*m/z*): 367.2 [MH^+].

Example 8

Dimethyl-[2-(2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-ethyl]-amine* (**8**)

According to the process described in Example 7, starting from 1-bromomethyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**4**) (0.20 mmole) and 2-dimethylamino-ethylchloride-hydrochloride (2.85 mmole), an oily product was obtained;

^{1}H NMR (ppm, $CDCl_3$): 2.39 (s, 6H), 2.69-2.72 (t, 2H), 3.83-3.87 (t, 2H), 4.79 (s, 2H), 7.35-7.89 (m, 8H);

MS (*m/z*): 353.2 [MH^+], 375.2 [MNa^+].

Example 9

Dimethyl-[2-(11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-ethyl]-amine* (**9**)

According to the process described in Example 7, starting from 1-bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**5**) (0.18 mmole) and 2-dimethylaminoethylchloride-hydrochloride (2.56 mmole), an oily product was obtained;
MS (*m/z*): 387.65 [MH^+].

Example 10

Dimethyl-[3-(11-chloro-2-oxa-8-thia-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-propyl]-amine* (**10**)

According to the process described in Example 7, starting from 1-bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene (**5**) (0.18 mmole) and 2-dimethylaminopropylchloride-hydrochloride (2.56 mmole), an oily product was obtained;
MS (*m/z*): 401.65 [MH^+].

Example 11

Dimethyl-[2-(2,8-dioxa-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-ethyl]-amine* (**11**)

According to the process described in Example 7, starting from 1-bromomethyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene (**6**) (0.25 mmole) and 2-dimethylamino-ethylchloride-hydrochloride (3.42 mmole), an oily product was obtained;
MS (*m/z*): 337.2 [MH^+].

Example 12

Dimethyl-[3-(2,8-dioxa-1-aza-dibenzo[e,h]*azulen-3-ylmethoxy)-propyl]-amine* (**12**)

According to the process described in Example 7, starting from 1-bromomethyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene (**6**) (0.25 mmole) and 2-dimethylamino-propylchloride-hydrochloride (3.42 mmole), an oily product was obtained;

MS (*m/z*): 351.2 [MH^+].

Preparation of Starting Compounds

11H-dibenzo[b,f]*thiepin-10-one oxime*

11H-dibenzo[*b,f*]thiepin-10-one (J.O. Jilek et al. *Mh. Chem.* **96** (1965) 182-207) (2.21 mmole) was dissolved in absolute ethanol (4.26 mL) and water (1.28 mL) under stirring and gentle heating. To the solution of ketone, aminehydroxide hydrochloride (4.42 mmole) and sodium acetate (4.42 mmole) were added. The reaction mixture was stirred and heated under reflux for 2 hours. After the completion of the reaction, 30 % ethanol (2 mL) was added into the hot reaction mixture and it was left to cool to room temperature. If no precipitation occurred, the solvent was evaporated under reduced pressure and the residue after evaporation was dissolved in water, extracted with dichloromethane, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

^1H NMR (ppm, $CDCl_3$): 3.65 (bs, 1H), 4.34 (s, 2H), 7.18-8.06 (m, 8H);

MS (*m/z*): 242.0 [MH^+], 264.0 [MNa^+], 296.0 [MNa^+ + MeOH].

8-chloro-11H-dibenzo[b,f]*thiepin-10-one oxime*

11-chloro-11H-dibenzo[*b,f*]thiepin-10-one (J.O. Jilek et al. *Mh. Chem.* **96** (1965) 182-207) (1,47 mmole) was dissolved in absolute ethanol (2.84 mL) and water (0.9 mL) under stirring and gentle heating. To the solution of ketone, aminehydroxide hydrochloride (2.95 mmole) and sodium acetate (2.95 mmole) were added. The reaction mixture was stirred and heated under reflux for 2 hours. After the completion of the reaction, 30 % ethanol (1 mL) was added into the hot reaction mixture and it was left to cool to room temperature. If no precipitation occurred, the solvent was evaporated under reduced pressure and the residue after evaporation was dissolved in water, extracted with dichloromethane, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;

MS (*m/z*): 276.45 [MH^+].

11H-Dibenzo[b,f]*oxepin-10-one oxime*

11H-dibenzo[*b,f*]oxepin-10-one (I. Ueda et al. *Chem. Pharm. Bull.* **23** (10) 2223-2231 (1975)) (4.42 mmole) was dissolved in absolute ethanol (8.52 mL) and water (2.56 mL) under stirring and gentle heating. To the solution of ketone, aminehydroxide hydrochloride (8.84 mmole) and sodium acetate (8.84 mmole) were added. The reaction mixture was stirred and heated under reflux for 2 hours. After the completion of the reaction, 30 % ethanol (4 mL) was added into the hot reaction mixture and it was left to cool to room temperature. If no precipitation occurred, the solvent was evaporated under reduced pressure and the residue after evaporation was dissolved in water, extracted with dichloromethane, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. After purification by chromatography on a silica gel column, a crystalline product was isolated;
MS (*m/z*): 226.0 [MH^+].

Table 1

Compound	Structure	Name
1a		3-Methyl-3,3a-dihydro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ol
2a		11-Chloro-3-methyl-3,3a-dihydro-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulen-3-ol
3a		3-Methyl-3,3a-dihydro-2,8-dioxa-1-aza-dibenzo[*e,h*]azulen-3-ol
1		3-Methyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene
2		11-Chloro-3-methyl-2-oxa-8-thia-1-aza-dibenzo[*e,h*]azulene
3		3-Methyl-2,8-dioxa-1-aza-dibenzo[*e,h*]azulene

4		3-Bromomethyl-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulene
5		3-Bromomethyl-2,8-dioxa-1-aza-dibenzo[*e*,*h*]azulene
6		3-Bromomethyl-11-chloro-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulene
7		Dimethyl-[3-(2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-propyl]-amine
8		Dimethyl-[2-(2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-ethyl]-amine
9		[2-(11-Chloro-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-ethyl]-dimethyl-amine
10		[3-(11-Chloro-2-oxa-8-thia-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-propyl]-dimethyl-amine
11		[2-(2,8-Dioxa-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-ethyl]-dimethyl-amine
12		[3-(2,8-Dioxa-1-aza-dibenzo[*e*,*h*]azulen-3-ylmethoxy)-propyl]-dimethyl-amine